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Micronutrient supplements for children after deworming

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Summary

The availability of a few inexpensive, single dose drugs to treat soil-transmitted helminths and schistosomiasis offers the potential to reduce a considerable burden of acute disease, especially among children sub-Saharan Africa. These treatments are being promoted as "rapid impact interventions". However, if helminth infections cause underweight, stunting, anaemia and impaired mental development in children, how will removing worms alone lead to recovery without treating the underlying deficits that have been caused or made worse by helminth disease? Energy, protein and micronutrients are required by children who are underweight or who have stunted growth; children who are anaemic will require iron and other micronutrients for haemopoiesis; and children who have lost education will need remedial teaching. Treating neglected worm diseases is an essential first step to good health, but anthelmintic drugs need to be integrated with simple and inexpensive nutritional interventions such as micronutrient supplements to promote recovery and have a rapid effect.

Introduction

The availability of a few inexpensive, single-dose drugs to treat several very common but neglected parasitic worm infections has created a flush of optimism that a large burden of ill-health and disability in Africa could be greatly reduced[1]. The benzimidazole derivatives albendazole and mebendazole are effective to different degrees against the three main species of soil-transmitted helminths[2] listed in Table 1, while the three main species of blood fluke that cause schistosomiasis can be treated with praziquantel (Table 1). All three drugs can be administered as a single dose treatment, either as a fixed amount in the case of albendazole or mebendazole, or as a single dose adjusted according to body weight in the case of praziquantel. To simplify matters further it has been shown possible to estimate the dose of praziquantel based on height so that a marked pole can be used to determine the number of tablets.[3] A tablet pole removes the need for expensive and fragile weighing scales and enables even illiterate people to give treatment if the number of tablets is represented as pictograms on the pole. The need is now to buy and deliver these treatments to people who require them, mostly children in sub-Saharan Africa, and thereby make a contribution to Millennium Development Goals.[4]

Several recent articles promoting the control of neglected parasitic diseases have referred to evidence of the effects of treatment on anaemia, child growth and mental development, and have used this to support the case for intensifying efforts to deliver anthelmintic drugs.[1,5-7] Some of these articles have called such treatments "rapid impact interventions".[1,7] There is no doubt that periodic treatment with effective anthelmintic drugs will greatly reduce parasite loads, alleviate acute disease, and help to reduce transmission. But the assumption that simply treating soil-transmitted helminths and schistosome infections will lead automatically and rapidly to better health, nutritional status and educational development is flawed and could create overly optimistic expectations.

If soil-transmitted helminths and schistosomes cause anaemia, how will the haemoglobin concentration increase after the worms have been killed without enough iron and other micronutrients in the diet? [5] If moderate or heavy infections with helminths cause a loss of appetite, malabsorption and maldigestion,[8] depending on the species, so that children become underweight or stunted, how will they achieve catch-up growth after treatment without enough energy, protein and micronutrients? And if worms have impaired children's education, how will they make up for the lessons that they have missed because they were absent from school or unable to concentrate properly, without remedial teaching?[9] These are not just rhetorical questions for the sake of argument, they identify concurrent deficits that need to be treated at the same time as anthelmintic drugs are given to children.

The effects of worms on nutritional status

All three major species of schistosomes that infect humans, both species of hookworms, and the whipworm (Table 1) contribute to blood loss, but in different ways. The passage of the eggs of *Schistosoma mansoni* and *S.japonicum* through the gut wall causes blood loss[5] that can, in moderate to heavy infections, be reported as dysentery,[10,11] although there is the possibility that some of the iron in haemoglobin may be reabsorbed in the lower intestine. This is not the case for *S. haematobium*: the iron in haemoglobin that passes into the bladder is lost in the urine (figure 1), and a milligram or more of iron a day may be urinated away each day.[12] It has been pointed out that the amount of iron lost by children infected with *Schistosoma haematobium* may be similar to daily menstrual losses of iron averaged out over a month.[8] The feeding of hookworms and the anti-coagulant they produce causes blood loss into the small intestine, some of which may be reabsorbed proximally.[13] Finally, moderate to heavy infections with *Trichuris trichiura* cause inflammation of the lower bowel, blood loss and dysentery.[14]

Figure 1 Urine specimens from schoolchildren in Tanzania showing macro and microhaematuria caused by *Schistosoma haematobium*.

For all these worms, the key nutrient lost is iron. This micronutrient is particularly hard to obtain in the diet and, once consumed, it is difficult to absorb. Meat is a better source of iron than plant foods, but perhaps only 20 – 30% of the iron already incorporated into the haem molecule is absorbed, compared with less than 10% of the iron present in vegetable foods because it is irreversibly bound to phytates and tannins.[15] However meat is a relatively expensive food for poor people, if it is eaten at all, and most dietary iron comes from plant foods. Although malaria, the hookworms and schistosomiasis all contribute to anaemia in people in sub-Saharan Africa, the dietary availability of iron is the major determinant of anaemia in countries such as Tanzania.[16] Even if there is internal bleeding due to worms, lost haemoglobin can be replaced up to a point if the intakes of iron and other nutrients are adequate.[17] But not all anaemia is caused by an iron deficiency either: a lack of micronutrients such as folate, vitamin B_{12} and vitamin A can also contribute to a low haemoglobin concentration.[18]

The role of both iron and vitamin A in anaemia were shown clearly in a placebo controlled, randomised trial in Tanzania in which supplements were given to children after deworming.[19] Schoolchildren living in coastal Tanzania were treated for soil-transmitted helminths and schistosomiasis and then randomly assigned to one of four groups to receive on 3 days a week one of the following treatments: 5,000 IU of vitamin A and 200 mg of ferrous sulphate; 5,000 IU of vitamin A alone plus an iron placebo; 200 mg of ferrous sulphate plus a vitamin A placebo; or both placebos.[19] After 12 weeks of treatment the haemoglobin concentration of children given both placebos, which is equivalent to being dewormed alone, increased significantly from the baseline measurement, but only by 3.6 g/L (95% CI 1.2 – 6.1); the group given vitamin A alone increased by 13.5 g/L (11.0 – 16.0); the group given iron alone increased by 17.5 g/L (15.0 – 20.0) and the group given both vitamin A and iron increased by 22.1 g/L (CI 19.6 – 24.6).[19] All increases were statistically significant compared with baseline measurements ($P \leq 0.001$) but the gain in haemoglobin concentration of the group given both micronutrients represented a 21% increase in only 3 months compared with about a 4% increase in the placebo group over the same period.[19] The children given both vitamin A and iron also gained 0.9 kg in weight (I 0.7 – 1.0) compared with only 0.2 kg (0.1 – 0.4) by the placebo group ($p < 0.001$), and they gained significantly more height as well in only 12 weeks ($p < 0.001$).[19] This indicates that treating worm infections and micronutrient deficiencies together may lead rapidly to improved growth, both ponderal and linear, as well as to an improved haemoglobin concentration.

Several studies have shown significant extra weight gain or linear growth among children who have been treated for worm infections alone[20-23] but other studies have not[24-26], which has created some perplexity about the inconsistency of findings. Some of this could be due to the fact that soil-transmitted helminths and schistosomes tend to be unevenly distributed between hosts (Figure 2) so that 80% of all worms may be found in 40% or fewer people. [27] This clumped or aggregated distribution means that the beneficial effects of deworming may be felt by only a minority of children in the short term, and the impact on the group average will be diluted.[28] But as two-thirds or more children may become moderately or heavily at least once during

a programme of periodic treatment and reinfection,[29] the effects of deworming may take some time to become apparent in any population of children. Even if studies of the impact of deworming have adequate controls, a sufficient sample size, repeated periodic treatment, and long enough follow-up, the mixed or inconclusive results noted in a recent review of deworming trials[30] could be due to the expectation that anthelmintic treatment alone will be sufficient. If treating worms increases appetite, as some studies have shown,[31-33] then there can only be increased growth if there is enough protein and energy to fuel that growth, and if there are no concurrent deficiencies of micronutrients as well. Supplements of multiple micronutrients alone may be sufficient to achieve improvements in the growth of young children in developing countries,[34] so the quality of the diet is important as well as quantity.

As well as removing a constraint on normal rates of growth by deworming, an additional question is can treating worms stimulate a greater than normal increase to achieve catch-up growth? There is good evidence of the potential for catch-up growth by malnourished children[35] but is difficult to assess whether it has been achieved without knowing what is the potential for growth in the first place, and without having untreated controls. Untreated controls are not easy to achieve, especially in the case of severe helminth disease, such as *Trichuris* dysentery syndrome. But children with this syndrome have been shown to experience rates of linear growth of nearly 11 cm/year after treatment, which is more than two standard deviations above the gain expected by British children of the same age.[36]

Figure 2 187 *Ascaris lumbricoides* recovered from a 5-year-old child in Bangladesh

The effect of worms on children's mental development

There is considerable interest in whether helminth infections can impair children's mental development and educational achievements.[9,37] Some consequences could be due to absenteeism from school due to illness or to effects on concentration, but others could be mediated through nutrition and the role that micronutrients such as iodine and iron have on the development of the brain and its functioning.[9,37-40] If helminths impair mental function and learning,

then perhaps treatment could lead to better cognitive and educational outcomes.

The main problem is that studies cited as evidence for effects of helminth infections or malnutrition on cognitive function, educational achievement or attendance are based on associations observed in cross-sectional data[41-43], which are open to confounding. The cognitive or educational deficits being measured in such studies are very likely to reflect the poverty and deprivation of children that occurs concurrently with chronic helminth infections and malnutrition, and cannot be considered as causative.

There have been a few trials of the effect of deworming on tests of cognitive function or educational achievement[44-49], but the results have not been consistent.[30] Again, this could because of the assumption that the impact of worms is reversible by treatment alone. But if children have missed lessons or been unable to concentrate properly at school because of their worm infections, recovery is likely to require remedial education in the same way that stunted children need remedial food and anaemic children need remedial micronutrients. Ideally if children in developing countries are to make best use of their opportunity for education they will need to be healthy from the start of schooling.

Conclusions

The idea that providing treatments for neglected parasitic infections such as soil-transmitted helminths and schistosomiasis are "rapid impact interventions"[1,7] may not be true for nutritional status, growth and educational achievements unless any deficits caused by these infections are treated at the same time, ideally in an integrated programme to keep delivery costs as low as possible. If they are not, the impact of deworming on growth and micronutrient status may take so long to achieve that the benefit of treatment may not be readily apparent, and this may affect support for programmes from governments and communities alike. The role of community directed treatment with ivermectin in the African Programme for Onchocerciasis Control has been important to sustain the programme because it is based partly on support from villagers who appreciate the relief from treating onchodermatitis.[50] Having quick and evident effects may be critical to sustaining deworming programmes.

How can remedial treatments for these deficits be delivered after deworming? First the "rapid impact package" [7] needs to provide remedial micronutrient supplements after treatment. Large therapeutic doses of vitamin A are inexpensive and easy to give, and anthelmintics are now being given at the same time as vitamin A to young children in many countries in Africa and Asia.[51] But neither anthelmintic drugs nor vitamin A should be taken by women in the first trimester of pregnancy because of potential teratogenicity,[52,53] which raises concern for treating adolescent girls. A study of 9,000 school children in grades 4 to 6 in Tanzania found that 20% of girls reported having had sex, but only 39% of 114 girls with biological markers of sexual activity such as an infection, acknowledged having had sex, indicating that such activity was greatly under-reported.[54] In an analysis of official education statistics,

pregnancy was reported to be a cause of school drop out for 6 or 7 girls per 1,000 in grades 6 and 7 respectively, also in Tanzania.[55] These data should provide a warning to programmes that give mass treatment with anthelmintic drugs to school-age children as well for those considering adding mega-dose supplements of vitamin A. The alternative, for vitamin A at least, is to give small daily doses.

In sharp contrast to vitamin A, iron is poorly absorbed and large or quickly repeated doses have side effects, so it has to be trickled into the body. To do this it will be necessary to give a course of iron supplements immediately after treatment, which provides an opportunity to give safe amounts of vitamin A, as well most other micronutrients including zinc, folate and iodine. The cost of the multiple micronutrient tablet developed by UNICEF for recent trails is currently about USD 0.01, which could be reduced by large scale purchases.[56] Providing micronutrient supplements was ranked by the Copenhagen Consensus as the second highest of 17 potential development interventions[57] mainly because of the high benefit to cost ratios which ranged from 4 – 43 for giving vitamin A to young children and from 176 – 200 for giving iron *per capita*.[58] Multiple micronutrient supplements may bring their own benefits but have an even greater potential to improve health when given after anthelmintic treatments.

Achieving good compliance in taking a course of micronutrient supplements will be less easy than for a single dose treatment, but randomised cluster trials in Mali and the Philippines have shown that school teachers can give weekly iron supplements for 12 weeks.[59,60] Keeping the iron load as low as possible may be important in the light of the risk of exacerbating infectious diseases indicated by a recently halted study in Zanzibar.[61] But in Zanzibar the iron was given daily to infants and very young children, so twice weekly supplements may be better tolerated by older children and have less effect on malaria, which is perhaps the main concern.[62] Nevertheless, the issue needs to be monitored during programmes in the same way that it is good practice to monitor the development of anthelmintic resistance.

The need for remedial energy and protein is much harder to deal with because school feeding programmes can be very expensive in comparison with the cost of drug treatments. The World Food Programme estimate that it costs an average of USD 34 a year to feed a child, or about 19 US cents/child a day.[63] This is expensive compared with costs of less than USD 1/year for delivering albendazole and praziquantel to schoolchildren in Ghana and Tanzania (figure 3).[64] But there are models other than a centrally organised programme in which food is imported and transported to schools to be cooked and given to children. For example, cash can be used to purchase food locally to prepare snacks at schools, an initiative in Indonesia that has also helped to support local farmers and community groups who prepare and sell food for school children.[65] In a small way perhaps, such programmes are an approach to addressing both ill-health and poverty in an integrated way. However, the relatively high costs of giving supplementary food, the lack of evidence of an effect on children's growth,[66] and the possibility of substitution for food given at

home will always be issues, so school feeding is unlikely to be feasible after deworming.

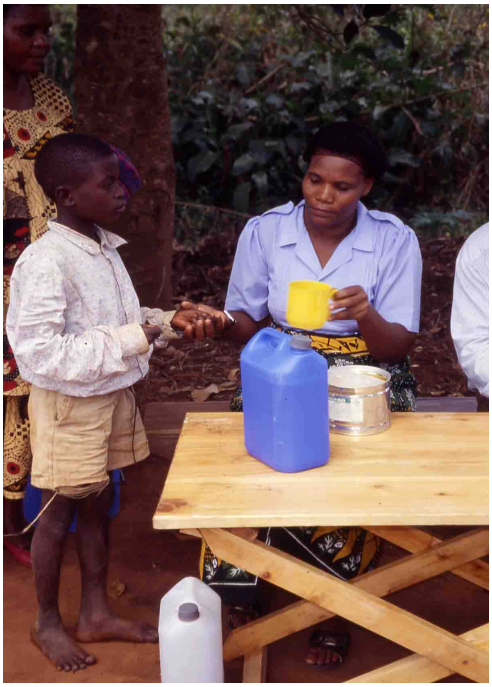

Figure 3 A schoolchild in Tanzania being given praziquantel as part of a mass treatment programme in schools

Remedial education may not be so hard to provide, given that children who benefit from anthelmintic treatments provided in school are enrolled in education. Nevertheless, if schools are to be conduit for anthelmintic treatments and micronutrient supplements, teachers need to be aware that they may need to provide remedial education to children after they have been treated and are recovering their health.

The final conclusion is not just that vertical disease control programmes and vertical nutrition programmes need to be integrated but, better still, that they should be reorientated to become horizontal: the aim should be to meet the needs of school-age children, a neglected age group that harbours a large burden of disease due undernutrition and neglected infections. To provide micronutrient supplements after deworming would be a good start, and such a programme offers the potential to contribute not only to Millennium Development Goals that combat major diseases and alleviate hunger, but also to contribute to the goal of ensuring that all children enrol in school and complete a basic education.

Table. The prevalence of some major neglected parasitic infections, the millions estimated to be at risk and infected,[67,68] and the main single dose treatments available.[69]

Disease	Causative organisms	Common name	Millions		Treatments	Single dosage
			At risk	Infected		
Soil-transmitted helminths	*Ascaris lumbricoides*	Large roundworm	4,211	1,221		
	Trichuris trichiura	Whipworm	3,212	795	Albendazole	400 mg
	Necator americanus	Hookworm	3,195	740	Mebendazole	500 mg
	Ancylostoma duodenale					
Schistosomiasis	*Schistosoma mansoni*	Blood flukes	393	54	Praziquantel	40 mg/kg
	Schistosoma haematobium		436	112		
	Schistosoma japonicum		45	1.7		

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